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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,672	02/07/2001	Hsu Ching-Hsaing	12774-002001	4367

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/778,672	Applicant(s) CHING-HSAING ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Claims 24-45 are pending in the application and under current examination.

Priority

This application was filed February 7, 2001.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing IgE level and reducing bronchopulmonary congestion upon subsequent allergen challenge by *oral* administration of a recombinant bacterium expressing a dust mite allergen, wherein the bacterium is derived from a non-pathogenic gram-positive bacterium selected from the group consisting of *Lactobacillus*, *streptococcus* or *Bifidobacterium*, does not reasonably provide enablement for doing so for *any* aeroallergens, by *any* route of administration using *any* strain of gram-positive bacteria. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

Claims are drawn to a method for decreasing IgE level and reducing bronchopulmonary congestion upon subsequent allergen challenge by administration of a recombinant bacterium expressing a dust mite allergen or an aeroallergen. Given the broadest reasonable interpretation, the claims embrace any route of administration, any aeroallergen, and any strain of non-pathogenic gram-positive bacterium.

The specification teaches the members of the genus *Lactobacillus* and dust mite allergens. The specification teaches that aeroallergen is airborne particles that can cause respiratory, cutaneous, or conjunctival allergy including dust mite and ragweed pollen. The exemplified embodiment is for the aeroallergen is the dust mite Der p5, p1, and p2 expressed by *Lactobacillus*, and oral vaccination. The specification does not teach the genus of non-pathogenic gram-positive bacterium, nor other routes of vaccine administration, or other types of aeroallergen.

In view of the state of the art and levels of the skilled in the art, *Kailasapathy* (Immunol and Cell Biol 2000;78:80-88) teaches that commonly used probiotic organisms are genus of *Lactobacillus*, *streptococcus* or *Bifidobacterium,* whereas the non-pathogenic gram-positive bacterium encompasses hundreds and thousands of

bacterial strains, it is unclear and unpredictable whether all of them are suitable for use as a vaccine carrier. The specification fails to teach or address this aspect of the claimed invention, thus, fails to provide an enabling disclosure commensurate with the scope of the claims.

Kailasapathy teaches that the probiotic bacterium *Lactobacillus*, or *Bifidobacterium* belong to normal micro flora of gastrointestinal system, therefore, are natural medicine for human health. It is not surprising that they could be used as a vaccine carrier for oral delivery. However, it is contrary to the common knowledge if these recombinant bacteria are delivered via other routes without triggering a significant host immune response. Therefore, it is highly unpredictable the consequence of using other routes of delivery of the recombinant bacteria. The specification fails to teach or address this aspect of the claimed invention, thus, fails to provide an enabling disclosure commensurate with the scope of the claims.

Airborne particles encompass broad range of compounds, from dust mite, to various pollens, to industrial residues, for example. These particles differ in structures and physical characteristics, from one example of dust mite allergen, one skilled in the art could not envision whether the method is suitable for other airborne particles. The specification fails to teach or address this aspect of the claimed invention, thus, fails to provide an enabling disclosure commensurate with the scope of the claims.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the teaching and working examples provided, and the breadth of the

claims that it would require undue experimentation to practice the invention commensurate to its scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24, 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of the claim recitation "the allergen is administered orally" or "the allergen is administered as a yogurt". Claim 24 is drawn to a method of administering a recombinant bacterium expressing an allergen, whereas claims 34 and 35 could read on administering the allergen directly, thus, the metes and bounds of the claims are unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 25, 28-34, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Hsu et al* (US 5,958,891), in view of *Medaglini et al* (PNAS 1995;92:6868-72, IDS/AI).

Claims are drawn to a method of decreasing the production of IgE, decreasing skin and airway inflammation, and decreasing bronchopulmonary congestion in a subject comprising administering to a subject a non-pathogenic, Gram-positive bacterium that comprises a nucleotide sequence encoding a dust mite allergen and a promoter operably linked to the nucleotide sequence, wherein the allergen-specific IgE production is suppressed upon subsequent exposure to the allergen; wherein the preferred bacterium is the genus of *Lactobacillus*, *streptococcus* or *Bifidobacterium*, wherein the dust mite allergen is selected from the group consisting of *Dermatophagoides pteronyssinus*, preferably a Der p5 allergen, a protein allergen, or any aeroallergen; wherein the promoter is a constitutive promoter, wherein the administration is orally, preferably in the form of a yogurt; wherein the subject is a human subject.

Hsu et al teach a method of suppressing the allergen-specific IgE production in a subject comprising administering to the subject a recombinant plasmid comprising a CMV promoter (constitutive) operably linked to a sequence encoding an allergen and administered via intramuscular, intranasal, and intratracheal routes (abstract), preferably dust mite *Dermatophagoides pteronyssinus* Der p5 allergen via intramuscular

injection (paragraph bridging columns 3 & 4), wherein upon subsequent challenge with allergen Der p5 i.p. or i.h., a 90% reduction of IgE was observed in the treated group compared to the controls (column 8, lines 24-38), wherein the allergen could also be Sj26 (*Schistosoma japonicum* protein 26), wherein the subject is a human subject (claims 3 and 8). *Hsu et al* also teach that the vector administration could suppress allergen-induced airway inflammation and bronchopulmonary congestion upon aerosol Der p5 exposure (paragraph bridging columns 9-10) and skin inflammation (column 11, section B). *Hsu et al* do not teach using a Gram-positive bacterium as the expression vehicle.

Medaglini et al teach a system that allowed for the stable expression of a wide range of protein antigens on the surface of non-pathogenic Gram-positive commensal bacteria by transforming the bacterium with a recombinant plasmid pSMB7 (abstract and right column on page 6870). The exemplified embodiment of the system is *Streptococcus gordonii* engineered to surface express an allergen from hornet venom (M6 protein). They administered the recombinant bacterial construct to mice orally and intranasally, and induced significant IgA and IgG immune response to the specific allergen. They further teach the development of the system is to circumvent the need to engineer pathogenic microorganisms, and the antigen/allergen could be steadily expressed extrachromosomally in the recombinants *in vitro* and *in vivo*, thus, the system is suitable for use as a carrier for wide range of antigens (Discussion). *Medaglini et al* do not teach particularly a dust mite allergen.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Medaglini et al,* by simply substituting the plasmid pSMB7-M6 with the pCMV-Der p5 as taught by *Hsu et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the non-pathogenic bacterial system could express the allergen stably, and using oral delivery route is less painful for patients. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 24-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Hsu et al* (US 5,958,891) and *Medaglini et al* (PNAS 1995;92:6868-72) as applied to claims 24, 25, 28-34, 43 above, and further in view of *Casas et al* (US 6,100,388) and *Kailasapathy et al* (Immunol and Cell Biol 2000;78:80-88).

Hsu et al and *Medaglini et al* do not teach using the *Lactobacilus acidophilus* or *bifidobacterium* genus as vaccine vehicles, and do not teach using milk products as carriers.

Casas et al teach using Lactobacilli transformed with a recombinant DNA expressing heterologous antigens as vaccine delivery vehicles, and the vaccine could be ingested orally in milk products (abstract), such as yogurt (column 1, line 49). *Casas et al* do not particularly teach a dust mite allergen.

Kailasapathy et al teach the therapeutic potential using probiotic organisms with particular emphasis on *Lactobacillus*, and *Bifidobacterium.* (see entire article particularly

abstract). They go on to teach that such therapeutic benefit has been shown in reduction of food allergy, i.e. reducing the extent and intensity of infant atopic dermatitis (left column, page 84).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Medaglini et al* and *Hsu et al* by simply substituting the *streptococcus* with *Lactobacillus*, and *Bifidobacterium* as taught by *Casas et al* and *Kailasapathy et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the vaccine could be easily delivered with milk products and proven to be effective for alleviating allergy. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
September 27, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER